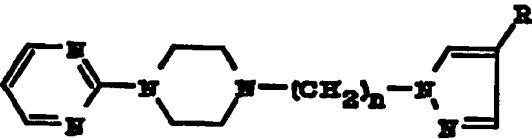
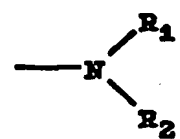


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(54) Title: USE OF ARYLPIPERAZINE DERIVATIVES FOR THE TREATMENT OF PARKINSON'S DISEASE AND PSYCHOSIS			
(57) Abstract			
<p>A method of treating drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis in which a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salts and metabolites thereof in which n is an integer from 1 to 6; and R represents H, halo, 1 to 4 alkyl, a heteroaryl group, sulphonyl, N-substituted or N,N-disubstituted sulphonyl, nitro, hydroxy, oxo, 1 to 4 alkoxy, cyano, 1 to 4 alkylcarboxylate, aryl or substituted aryl group, or amino or substituted amino group of formula (a), in which R₁ and R₂, which may be the same or different, represent H, alkyl, aryl, alkylcarbonyl, arylcarbonyl, alkylsulphonyl or arylsulphonyl, the alkyl fragments of these groups containing 1 to 4 carbon atoms, is administered in conjunction with a pharmaceutically acceptable diluent or carrier.</p>		 <p style="text-align: right;">(I)</p>	
		 <p style="text-align: center;">(a)</p>	

FOR THE PURPOSES OF INFORMATION ONLY

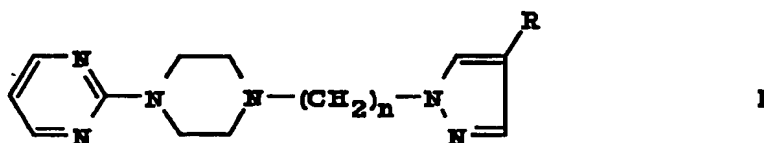
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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GA	Gabon				

use of arylpiperazine derivatives for the treatment of parkinson's disease and psychosis

This invention relates to the medical treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and
 5 psychosis.

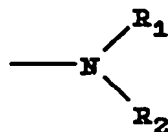
According to the present invention, there is provided a method of treating drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis in which a
 10 therapeutically effective amount of a compound of formula I



or pharmaceutically acceptable salts and metabolites thereof in which

n is an integer from 1 to 6; and

15 R represents H, halo, an alkyl group containing 1 to 4 carbon atoms, a heteroaryl group, sulpho, N-substituted or N,N-disubstituted sulphamoyl, nitro, hydroxy, oxo, an alkoxy group containing 1 to 4 carbon atoms, cyano, an alkylcarboxylate group containing 1 to 4 carbon atoms,
 20 an aryl or substituted aryl group, or an amino or substituted amino group of formula



in which

R₁ and R₂, which may be the same or different, represent H, alkyl, aryl, alkylcarbonyl, arylcarbonyl, alkylsulphonyl or arylsulphonyl, the alkyl fragments of these groups containing 1 to 4 carbon atoms

5 is administered in conjunction with a pharmaceutically acceptable diluent or carrier to a mammal in need thereof.

The terms "treatment" and "treating" as used in this specification include therapeutic and prophylactic
10 treatment.

A preferred compound of formula I is 2-([4-(4-chloropyrazol-1-yl)butyl]-1-piperazinyl)pyrimidine (Lesopitron) or a salt thereof.

The preparation and use of compounds of formula I,
15 such as 2-([4-(4-chloropyrazol-1-yl)butyl]-1-piperazinyl)pyrimidine and salts thereof in the treatment of anxiety is described in EP-A-382637. Their use in the treatment of withdrawal symptoms is described in EP-A-429360, and in the treatment of cognitive
20 disorders in EP-A-497658.

Other aryl-piperazine 5-HT_{1A} partial agonist anxiolytics (buspirone, gepirone) are antagonists of postsynaptic 5-HT_{1A} receptors in the CNS as demonstrated by their ability to reverse the increase in mobility in
25 the Porsolt test which is induced by the 5-HT_{1A} full agonist, 8-hydroxy-(2-di-N-propylamino)tetralin (Luscombe et al, 1993, 108 : 669-677). However, compounds of formula I have the surprising advantage that they do not show this antagonist action.
30 Therefore, unlike other aryl-piperazine anxiolytics, compounds of formula I are 5-HT_{1A} receptor agonists

which are devoid of antagonist activity and their effects on this receptor are not self limiting. This activity, coupled with the ability to inhibit dopaminomimetic behaviours and antagonise catalepsy, gives compounds of formula I utility in the treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis.

The present invention also includes the use of a compound of formula I in the manufacture of a medicament for use in the treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis.

The present invention also includes a pharmaceutical composition for treating drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis, comprising a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier.

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 500 mg preferably 1 to 100 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 100 mg of the active compound.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium

carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without
5 additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a
10 carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is
15 administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

20 Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may
25 comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the
30 pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential

transdermal accelerant such as dimethyl sulphoxide or propylene glycol. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

- 5 In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

10 The ability of compounds of formula I, such as 2-
 {[4-(4-chloropyrazol-1-yl)butyl]-1-piperazinyl}-
 pyrimidine, to treat drug-induced dyskinesias,
 Parkinson's Disease, dopaminomimetic psychosis in
 Parkinson's Disease and psychosis is indicated by the
 following tests, the results of which are given in
 Table 1.

15 Test 1

Antagonism of Apomorphine-Induced Climbing in Mice

20 Groups of 10 male mice weighing 18-35 g (max. range
 10 g) were treated with test compound or control vehicle
 by po administration. 30 minutes later, mice were
 injected sub-cutaneously with apomorphine (0.88 mg/kg).
 Immediately after the apomorphine injection the mice
 were placed in the test cages and the climbing behaviour
 of each mouse was assessed at 10 and 20 minutes on a
 simple 0-2 ranking scale.

- 25 The ED₅₀ values (dose causing 50% of the control
 score) for the test compounds and 95% confidence limits
 were calculated. ED₅₀ values are calculated as free base
 equivalents and given in Table 1.

Test 2Antagonism of Haloperidol-Induced Catalepsy in Rats

Groups of 5 male rats weighing 130-190 g were treated with haloperidol (0.125-4 mg/kg) by ip administration four hours prior to the final reading. Catalepsy was assessed at three timepoints. Lesopitron, buspirone, gepirone or control vehicle was administered po one hour prior to the final reading; 8-OH-DPAT or vehicle was injected subcutaneously 20 minutes prior to the final reading.

The ED₅₀ (dose causing 50% of the control score) for haloperidol was calculated in the presence and absence of test compound. The amount of test compound producing a parallel shift of significance $p < 0.05$ is given in Table 1.

Test 3Antagonism of 8-Hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT)-Induced Increases in Mobility in the Porsolt Test

8-OH-DPAT increases the mobility of mice in the Porsolt test (Porsolt et al, 1977, Arch Int Pharmacodyn Ther 229: 327-337; Luscombe et al, 1993, Br. J. Pharmacol. 108: 669-677).

Male mice weighing 21-29 g were administered po with test compound or control vehicle, then sc with 8-OH-DPAT (3 mg/kg) immediately thereafter, one hour prior to the initiation of the six minute mobility test. Movements of the mice were measured between 2 and 6 minutes after initiation of the test. The oral ED₅₀ value for antagonism of the 8-OH-DPAT effect by the test compounds is given in Table 1.

TABLE 1

Test Compound	Test 1 ED ₅₀ (mg/kg)	Test 2 ED ₅₀ (mg/kg)	Test 3 ED ₅₀ (mg/kg)
Lesopitron	261	50	>100
Buspirone	50.2	20	18
Gepirone	50.9	40	25
8-OH-DPAT	0.63 (sc admin)*	< 1 (sc admin)*	-

* compound administered sc because it is inactive orally.

- 10 In addition to being full agonists of 5-HT_{1A} receptors, compounds of formula I have a surprisingly long duration of action in the apomorphine-induced climbing test in mice (Test 1 described earlier) in comparison to other aryl-piperazine 5-HT_{1A} anxiolytics and the only other known full 5-HT_{1A} receptor agonist, 8-hydroxy-(2-di-N-propylamino)tetralin. Duration of action is illustrated by Test 4, the results of which are given in Table 2.

Test 4

- 20 Duration of Action of Antagonism of Apomorphine-Induced Climbing in Mice

- 25 Groups of 10 male mice weighing 18-35 g (maximum range 10 g) were treated with twice the ED₅₀ value (dose causing 50% of the control score in Test 1) of test compound by po or sc administration. At appropriate times between 30 minutes and 6 hours later, groups of mice were injected sc with apomorphine (0.88 mg/kg). Immediately after the apomorphine injection the mice were placed in the test cages and the climbing behaviour

of each mouse was assessed as in Test 1. The % inhibition of climbing behaviour was plotted against time from test compound dosing. The duration of action of the test compound was determined from the graph as the time at which there was 50% inhibition.

TABLE 2

Test Compound	Duration of Action (hours)	Administration
Lesopitron	4.00	oral
Buspirone	1.33	oral
Gepirone	2.00	oral
8-OH-DPAT	0.50	sc

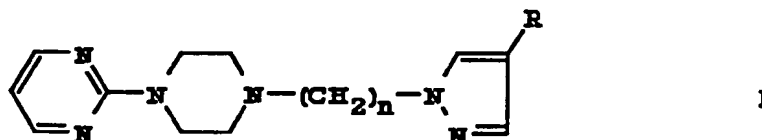
The full agonist, 8-OH-DPAT, has to be administered sub-cutaneously because it has no activity orally.

The results of Tests 1, 2 and 3 show the unexpected feature of compounds of formula I in that such compounds do not inhibit the mobility response to 8-OH-DPAT in mice as do other 5-HT_{1A} partial agonists, but they retain antagonist activity against both apomorphine-induced climbing in mice and haloperidol-induced catalepsy in rats. This activity makes compounds of formula I advantageously useful in the treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis.

The results of Test 4 show that Lesopitron has a surprisingly long duration of action and also can be administered orally. These two features make compounds of formula I advantageously useful in the treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis.

CLAIMS

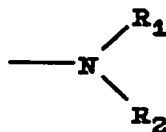
- 1) A method of treating drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis in which a therapeutically effective amount of a compound of formula I



or pharmaceutically acceptable salts and metabolites thereof in which

n is an integer from 1 to 6; and

- R represents H, halo, an alkyl group containing 1 to 4 carbon atoms, a heteroaryl group, sulpho, N-substituted or N,N-disubstituted sulphonyl, nitro, hydroxy, oxo, an alkoxy group containing 1 to 4 carbon atoms, cyano, an alkylcarboxylate group containing 1 to 4 carbon atoms, an aryl or substituted aryl group, or an amino or substituted amino group of formula



in which

- R₁ and R₂, which may be the same or different, represent H, alkyl, aryl, alkylcarbonyl, arylcarbonyl, alkylsulphonyl or arylsulphonyl, the

alkyl fragments of these groups containing 1 to 4 carbon atoms

5 is administered in conjunction with a pharmaceutically acceptable diluent or carrier to a mammal in need thereof.

10 2) The use of a compound of formula I in the manufacture of a medicament for use in the treatment of drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis.

15 3) A pharmaceutical composition for treating drug-induced dyskinesias, Parkinson's Disease, dopaminomimetic psychosis in Parkinson's Disease and psychosis, comprising a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/EP 95/01195

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP-A-0 497 658 (LABORATORIOS DEL DR. ESTEVE) 5 August 1992 cited in the application	3
A	see the whole document ---	1,2
Y	THE EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 255, no. 1-3, 1994 pages 185-196, HAJ-DAHMANE, S. ET AL 'INTERACTIONS OF LESOPITRON (E-4424) WITH CENTRAL 5-HT1A RECEPTORS: IN VITRO AND IN VIVO STUDIES IN THE RAT' see the whole document ---	1,2
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 June 1995

Date of mailing of the international search report

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Mair, J

INTERNATIONAL SEARCH REPORT

Intern. Pat. Application No

PCT/EP 95/01195

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NEUROPHARMACOLOGY, vol. 27, no. 5, 1988 pages 515-518, INVERNIZZI, R.W. ET AL '8-HYDROXY-2-(DI-N-PROPYLAMINO) TETRALIN, A SELECTIVE SEROTONIN1A RECEPTOR AGONIST, BLOCKS HALOPERIDOL INDUCED CTALEPSY BY ACTION ON RAPHE NUCLEI MEDIANUS AND DORSALIS' see the whole document ---	1,2
Y	PHARMACOLOGY AND TOXICOLOGY , vol. 64, 1989 pages 3-5, AHLENIUS, S. 'ANTIPSYCHOTIC-LIKE PROPERTIES OF THE 5-HT1A AGONIST 8-OH-DPAT IN THE RAT' see the whole document ---	1,2
A	NEUROLOGY, vol. 40, no. 5, 1990 pages 832-834, WOLTERS, E.C. ET AL 'CLOZAPINE IN THE TREATMENT OF PARKINSONIAN PATIENTS WITH DOPAMINOMIMETIC PSYCHOSIS' see the whole document -----	1-3

INTERNATIONAL SEARCH REPORT

I: ational application No.

PCT/EP 95/ 01195

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 1 is directed to a method of treatment of the human
body the search has been carried out and based on the alleged effects of th
e compound.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-497658	05-08-92	FR-A- 2671972	31-07-92
		AU-B- 646137	10-02-94
		AU-A- 1044592	30-07-92
		CA-A- 2059984	26-07-92
		JP-A- 4312529	04-11-92
		US-A- 5182281	26-01-93
